Raltegravir (RAL, Isentress)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 400 mg (poloxamer tablet)

Dosing Recommendations

Neonate/infant dose:
RAL is not approved for use in neonates/infants.

Pediatric dose:
RAL is not approved for use in children <16 years of age.

Investigational dose in children >6 years of age (and body weight >25 kg):
400 mg twice daily.

Adolescent (≥16 years of age)/adult dose:
400 mg twice daily.

Selected Adverse Events

- Nausea, diarrhea
- Headache
- Fever
- Creatine phosphokinase (CPK) elevation, muscle weakness, and rhabdomyolysis

Special Instructions

- Give RAL without regard to food.

Metabolism

- Uridine diphosphate glucotransferase (UGT1A1)-mediated glucuronidation.
- **Dosing of RAL in patients with hepatic impairment:** No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- **Dosing of RAL in patients with renal impairment:** No dosage adjustment is necessary.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Metabolism:* The major mechanism of clearance of raltegravir is mediated through glucuronidation by UGT1A1. Inducers of UGT1A1 such as rifampin and tipranavir may result in reduced plasma concentrations of raltegravir, while inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir.
- Before raltegravir is administered, the patient's medication profile should be carefully reviewed for potential drug interactions with raltegravir.

Major Toxicities:

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, and itching.
- *Less common:* Abdominal pain, vomiting, insomnia. Patients with chronic active hepatitis B and/or hepatitis C are more likely to experience worsening aspartate aminotransferase (AST), alanine

aminotransferase (ALT), or total bilirubin than are patients who are not coinfected.

- *Rare:* CPK elevations (Grade 2–4) have been observed in some patients. Myopathy and rhabdomyolysis have been reported. Use raltegravir with caution in patients receiving medications associated with these toxicities. Anxiety, depression, especially in those with prior history. Rash and Stevens-Johnson syndrome (SJS) have been reported. Thrombocytopenia.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/cgi-bin/INIResiNote.cgi).

Pediatric Use: Raltegravir is not approved by the Food and Drug Administration (FDA) for use in children <16 years of age. Raltegravir in combination with other antiretroviral (ARV) agents is currently being evaluated in IMPAACT 1066, a Phase I/II study in HIV-infected children, in which intensive pharmacokinetic (PK) evaluations were performed on Days 7–12 after raltegravir was added to a stable ARV backbone.

Because there is no food or fasting requirement with licensed use of raltegravir in adults, intensive PK evaluations were initially performed in children 12 to <19 years of age, with raltegravir administered with food[1]. However, because the effect of food made comparisons to data obtained in fasting adults difficult, the study was then amended to conduct PK evaluations in the fasted state. This led to selection of a dose of 400 mg twice daily of the approved formulation (poloxamer tablet) in children >12 to <19 years of age for longer term evaluation of safety and efficacy[2]. Preliminary data from 43 participants in this age group after 24 weeks of treatment with raltegravir plus an optimized background regimen demonstrated that 71% of participants had either a viral load <400 copies/mL or a 1.0 $_{\log}$ decrease in viral load; 53% had a viral load <50 copies/mL; and the median CD4 count increase was 111 cells/mm^3. Four Grade 3 adverse reactions (2 neutropenic episodes, 1 liver enzyme elevation, and 1 behavioral change) were judged possibly related to raltegravir; no participants discontinued therapy due to toxicity[3].

Children ≥6 to <12 years of age were initially treated at a dose of 8 mg/kg twice daily. Evaluation of the PK data in 10 participants again led to choosing a uniform dose of 400 mg twice daily for children who weighed >25 kg. At 12 and 24 weeks of therapy, 78% and 67% of 14 children in this cohort had a viral load <400 copies/mL[4]. No unusual toxicity has been seen so far[4-5].

In addition to the approved adult formulation (400-mg poloxamer tablet), two investigational raltegravir preparations are being evaluated in IMPAACT 1066: chewable ethylcellulose tablets in children >2 to <12 years of age[6] and an oral suspension for children <2 years of age. PK studies of the chewable tablet have been performed and long-term follow-up is ongoing[6-7].

In the French Expanded Access Program, 23 heavily treatment experienced youth 12–17 years of age who acquired HIV infection perinatally have been treated with raltegravir and other active agents, including etravirine and darunavir, with good virologic and immunologic results[8-9].

References

1. Acosta A, Wiznia A, Nachman S, et al. Raltegravir (RAL) pharmacokinetics (PK) in adolescents: Preliminary results from IMPAACT protocol 1066. Paper presented at: 9th International Workshop on Clinical Pharmacology of HIV Therapy; April 7-9, 2008; New Orleans, LA. Abstract P8.
2. Nachman S, Acosta E, Wiznia A, et al. Raltegravir phamacokinetics (PK) and safety in adolescents: Preliminary results from IMPAACT P1066. Paper presented at: 48th Interscience Conference on Antimicrobial Agents and Chemotherapy

(ICAAC); October 25-28, 2008; Washington, DC. Abstract H-4059A.

3. Nachman S, Samson P, Frenkel L, et al. 24 week safety and efficacy from IMPAACT P1066: A phase I/II, multicenter, open-label, noncomparative study to evaluate raltegravir (RAL) in HIV-1 infected youth. Paper presented at: 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 12-15, 2009; San Francisco, CA. Abstract H-924a.
4. Nachman S, Samson P, Acosta E, et al. Pharmacokinetic (PK), safety, and efficacy data on cohort IIA; youth aged 6 to 11 years from IMPAACT P1066: A phase I/II study to evaluate raltegravir (RAL) in HIV-1 infected youth. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA. Abstract 873.
5. Wiznia A, Samson P, Acosta E, et al. Safety and efficacy of raltegravir (RAL) in pediatric HIV infection. Preliminary Analysis from IMPAACT P1066. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 874.
6. Nachman S, Acosta E, Samson P, et al. Interim results from IMPAACT P1066: Raltegravir (RAL) oral chewable tablet (OCT) formulation in children 6 to 11 years. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA. Abstract 161LB.
7. Nachman S. Interim results from IMPAACT P1066: Raltegravir (RAL) oral chewable tablet (CT) formulations in children 2-5 years. Paper presented at: 18th Conference on Retroviruses and Opportunistic Infections (CROI); February 27-March 2, 2011; Boston, MA. Abstract 715.
8. Thuret I, Chaix ML, Tamalet C, et al. Raltegravir, etravirine and r-darunavir combination in adolescents with multidrug-resistant virus. *AIDS*. 2009;23(17):2364-2366.
9. Thuret I, Tamalet, C., Reliquet, V. Raltegravir in Children and Adolescents: The French Expanded Access Program. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 873.